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# Inhaled Corticosteroids for Asthma Therapy*

## Patient Compliance, Devices, and Inhalation Technique

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***Background:*** **Patient compliance, inhalation devices, and inhalation techniques influence the effectiveness of inhaled medications.**
***Methods:*** **This article presents the results of a systematic literature review of studies measuring compliance with inhaled corticosteroids, measuring inhalation technique with different inhalation devices, and estimating the proportion of inhaled drug that is deposited in the lung.**
***Results:*** **Overall, patients took the recommended doses of inhaled medication on 20 to 73% of days. Frequency of efficient inhalation technique ranged from 46 to 59% of patients. Education programs have been shown to improve compliance and inhalation techniques. The lung deposition achieved with different inhalers depends on particle size as well as inhaler technique.**
***Conclusion:*** **This review demonstrates that multiple factors may come between a prescription of an inhaled corticosteroid and the arrival of that medicine at its target organ, the lung.**
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**Key words:** asthma; compliance; inhaler technique; inhalers

**Abbreviations:** DPI = dry powder inhaler; ICS = inhaled corticosteroid; MDI = metered-dose inhaler

Asthma is a common chronic inflammation of the airways that causes periodic attacks of wheezing and troubled breathing. Pharmacologic therapy is used to prevent and control asthma symptoms and reverse airflow obstruction. The major classes of asthma medications are β-agonists, methylxanthines, anticholinergics, leukotriene modifiers, nonsteroidal anti-inflammatory drugs, and corticosteroids (glucocorticoids). The majority of these medications are inhaled, and their effectiveness in clinical practice can be affected by many factors.

In this article, we examined three factors that appear to have an effect on the effectiveness of inhaled corticosteroid (ICS) treatment by conducting a review of the relevant literature. First, we examined patient compliance with inhaled asthma therapy. Second, we examined inhalation technique. Third, we examined the impact of inhalation technique and inhalation device on drug deposition in the lungs. The main objective of the article was to summarize the research conducted so far into these three factors to provide information about the reliability of the inhaled route of administration of ICSs.

### Materials and Methods

The literature review started with a thorough key word search of the National Library of Medicine's MEDLINE database for articles on inhaled asthma therapy published between January 1966 and 1997. We examined the abstracts of these articles and identified articles that presented the results of studies of compliance, inhalation technique, and lung deposition of inhaled asthma drugs. We obtained these articles and examined their references for any other articles pertaining to these issues. We identified Australian and European articles from journals that are included in MEDLINE, such as *European Respiratory Journal*, *Medical Journal of Australia*, *Australian and New Zealand Journal of Medicine*, *European Journal of Respiratory Diseases*, and *Acta Allergologica*, as well as from international medical journals such as *Lancet*, *Asthma*, and *Respiratory Medicine*. From searching the references of the articles we obtained with the MEDLINE search, we found articles from European journals not listed in MEDLINE, such as *British Journal of Disease of the Chest*. In

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total, we retrieved and reviewed approximately 500 article abstracts as a part of our initial and follow-up review process. We found only 40 articles that reported the results of studies that met our inclusion criteria (as described below) in the areas of interest for this study.

### *Compliance*

According to Haynes et al,[1] compliance is "the extent to which a person's behavior (in terms of taking medications, following diets, or executing lifestyle changes) coincides with medical or health advice." The issue of noncompliance is complicated by different patterns of noncompliance and a variety of measurements of noncompliance. Cochrane[2] identifies several patterns of noncompliance, including taking only half of the medications at the prescribed times, taking the medication regularly for a period and stopping, and skipping prescribed doses. Compliance with preventive therapy such as ICSs whose effect is seen over a period of weeks may be less than compliance with drugs that relieve asthma symptoms more rapidly. Thus, we limited our review to studies reporting compliance rates for ICSs.

Several methods of measuring compliance are reported in the literature, including biochemical measures, patient diaries (self-reported), physician opinion, measuring the amount of drug used (weighing canisters or counting pills), or an electronic measuring device like a Turbuhaler Inhalation Computer or Nebulizer Chronolog (Medtrac Technologies, Lakewood, IL).[3-5] Biochemical measures, such as theophylline concentration (used to measure compliance with theophylline therapy), can be influenced by drug absorption, tissue distribution, and renal elimination.[6] Self-reports, patient diaries, and physician opinion overestimate compliance.[5,7,8] Compliance measured using canister weight can be distorted by episodes of canister dumping, or expelling medication into the air before evaluation, as evidenced in the study by Rand et al.[9] The study by Braunstein et al[5] measured compliance using several different methods and showed that patient self-report, physician rating, and canister weight all gave significantly higher estimates of patient compliance than the Nebulizer Chronolog electronic method. They concluded, as did other researchers, that, of the currently available methods for measuring compliance, the electronic measuring devices offer the most accurate and valid measurement of patient compliance.[4,5,9,10]

In evaluating compliance with ICSs, we limited our examination to studies using the Nebulizer Chronolog or the Turbuhaler Inhalation Computer. For this section of the report, we evaluated studies that reported results in terms of the fraction of days on which patients comply with treatment and the fraction of the prescribed quantity of drug used. We report the range of results based on the selected studies. Compliance is reported as a percentage of days of underuse and overuse as well as the ratio of doses taken to prescribed doses. Underuse is defined in these studies as a percentage of days when a patient takes fewer inhalations than prescribed or < 50% of the prescribed medication. Overuse occurs on days when patients take more than the prescribed number of inhalations. There was one published study estimating the impact of patient education on compliance using an electronic measure of compliance that is also included in our results table.

### *Inhalation Technique*

The effectiveness of inhaler therapy depends not only on compliance, but also on the inhaler technique. We included articles on inhaler technique regardless of the drug being inhaled inasmuch as our focus here was on the skills needed for proper inhalation. We used three different measures to examine the prevalence of suboptimal inhaler technique. First, we examined subjective physician assessments, in which the physician grades the inhalation technique, usually into three categories, such as "good," "adequate," and "inadequate." Second, we looked at studies that used a measure of "frequency of efficient technique" defined as an increase in $FEV_1$ that is ≥ 15%. Third, we examined the fraction of patients not complying with individual steps of proper inhaler use that have been identified in the research literature. For example, Manzella et al[11] have developed a set of 10 skill items for measuring proper use of the metered-dose inhaler (MDI). We also present the results of controlled studies of the effect of education on inhalation technique.

### *Lung Deposition*

For ICSs, the efficacy depends on the topical activity of the drug that reaches the target area, whereas the adverse events depend both on oral deposition and systemic activity. Systemic activity of the drug depends on the amount of the drug absorbed either through the GI tract or through the lungs, as well as on the first-pass metabolism for drug absorbed through the GI tract. The amount of drug delivered to the lungs depends on the inhalation technique,[12] as well as on the type of inhaler used and the fine particle dose of the drug.[13,14] The fine particle dose of the drug is defined as the fraction of particles with a diameter between 1 and 4 μm.[15]

In this study, we construct evidence tables of studies to examine the effect of the combination of inhalation technique, inhalation device, and particle size on the amount of drug reaching the target area. Deposition of the drug in the lung is measured either by labeling the test drug with radioactive technetium, mixing the test drug with radiolabeled nontherapeutic particles, or by measuring excretion of the drug at various times after inhalation.[13] When radioactive labeling is used, the lung is photographed and calculations made of the total and regional lung deposition. When drug excretion is measured, activated charcoal is used to prevent absorption of the drug from the GI tract.

## Results

### *Compliance*

Table 1 shows the results of studies that used an electronic measuring device to estimate compliance with ICSs in asthma patients. Overall, patients took the recommended doses of medication on 20 to 73% of days. The percentage of underuse days ranged from 24 to 69%. Overuse (2 to 23%) is much less frequent than underuse. Average compliance, measured as the ratio of the doses taken to those prescribed, ranged from 63 to 92%. The 92% compliance was observed in a study by van der Palen et al[16] and occurred after an intensive education program. Preeducation compliance in this study was 83%.

### *Inhalation Technique*

Table 2 shows the fraction of patients using each type of inhaler correctly on the basis of physician



**Table 1—*Compliance Articles: Inhaled Corticosteroids in Asthma*[a]**

| Factor | Coutts et al[10] | Mann et al[17] | Mann et al[17] | Mawhinney et al[18] | Brisley et al[3] | Apter et al[19] | van der Palen et al[16] | van der Palen et al[16] | Young et al[20] | Young et al[20] |
|---|---|---|---|---|---|---|---|---|---|---|
| Drug | Variety of ICSs | BDP | Fluticasone | Tiaceutol pivalate | Terbutaline/budesonide | Variety of ICSs | BDP | BDP | BDP | BDP |
| Electronic measuring device | NC | NC | NC | TIC | MDI Chronolog | NC | NC | NC | NC | NC |
| Patients | Children | Adults | Adults | Adults | Adults | Adults | Adults | Adults | Adults | Adults |
| Time | 1 mo | 9 wk | 6 wk | 3 wk | 12 wk | 6 wk | 2 wk (preeducation) | 4 wk (postreduction) | 3 wk | 2 wk |
| Country | UK | US | US | US | UK | US | Holland | Holland | UK | UK |
| Number of patients | 14 | 10 | 8 | 15 | 102 | 50 | 21 | 21 | 11 | 9 |
| Dose | Unspecified | qid | bid | qid | bid | bid | Unspecified | Unspecified | Unspecified | Unspecified |
| Average compliance ± SD, % | | 67 ± 30 | | | 86 ± 20 | 63 ± 39 | 83 ± 39 | 92 ± 52 | 78 ± 30 | 70 ± 14 |
| Underuse days, % | 55† | 69† | 37† | 56† | 39–49† | | 24§ | 27§ | | |
| Overuse days, % | 2† | 11† | 22† | 23† | 7–8† | | 3‖ | 10‖ | | |

[a] Average compliance defined as doses taken/doses prescribed; BDP = beclomethasone dipropionate.
† Under (over) use defined as the percentage of days when patients took fewer (more) than the prescribed number of inhalations.
‡ Underuse defined as the percentage of days patients took less than 50% of the prescribed dose.
§ Underuse defined as the percentage of days when patients took fewer than 75% of the prescribed number of inhalations.
‖ Overuse defined as the percentage of days patients took more than 125% of the prescribed dose.



assessment or frequency of efficient technique. The subjective physician assessments vary widely regarding the adequacy of inhaler technique. "Good" inhaler technique for MDI and Rotohaler ranged from 5%[7] to 86%[24] of patients. Training in the use of the inhaler greatly increased "good" technique in two studies, from 6 to 46% in the study by Horsley and Bailie[23] and from 28 to 52% in that of Cayrard and Orehek.[25] Frequency of efficient technique ranged from 46 to 59% of patients.

Table 3 lists the percentage of patients not complying with individual tasks on the inhaler task list. Lack of coordination of inhaler activation and onset of inspiration ranges from 17 to 68% for the MDIs. Other tasks are not performed correctly by a significant proportion of patients, including expiration before inhaling, inhaling deeply, and holding breath at the end of the inspiration. A study by Bailey et al[32] showed that only 10% of patients did all 10 skills and 48% did eight or more skills on a checklist for MDI use correctly before a self-management education program. After the program, these percentages increased to 52% and 95%, respectively. A study by Goodman et al[30] in 59 adults used a specially developed computerized device to directly measure four skills associated with good MDI technique. These were inspiratory airflow rate, coordination of actuation with inspiration, holding breath at the end of inspiration, and an acceptably deep inspiration. These skills were not correct in 42%, 47%, 24%, and 39% of the adults, respectively.

### *Lung Deposition*

Tables 4, 5 show the amount of drug delivered to the target area for different types of inhalers and drugs. Studies have compared the amount of drug deposited in the lungs using dry powder inhalers (DPIs) and the MDI. A study comparing MDIs and DPIs found an improvement in lung deposition of terbutaline from 8% with the MDI to 22% with the DPI.[37] However, two studies using salbutamol[35,36] showed a lower rate of lung deposition with the DPI compared with the MDI.

The use of large-volume spacers can also improve drug delivery to the lungs.[13] Newman et al[33] found, with an MDI, 9% deposition in the lungs and 81% deposition in the oropharynx of a radiolabeled nontherapeutic particle. When a spacer was used, lung deposition increased to 21%, the oropharyngeal deposition decreased to 17%, and 56% remained in the spacer. However, another study found similar lung deposition from an MDI, with or without a spacer device.[35] The study by

Table 2—*Proper Inhalation Technique**

| Study | No. | Year | Trained | Type of Inhaler | Physician Assessment, % | | | Frequency of Efficient Technique, % |
|---|---|---|---|---|---|---|---|---|
| | | | | | "Good" | "Adequate" | "Inadequate" | |
| Dompeling et al[7] | 41 | 1992 | Yes | Rotohaler | 5 | 68 | 27 | |
| Hilton[20] | 62 | 1990 | NS | Rotohaler | 50 | 29 | 21 | |
| Pedersen et al[21] | 39 | 1986 | Yes | Rotohaler | | | | 46 |
| Hilton[20] | 262 | 1990 | NS | MDI | 45 | 25 | 30 | |
| Crompton[28] | | 1990 | Yes | MDI | | | | 50 |
| Pedersen et al[21] | 132 | 1986 | Yes | MDI | | | | 46 |
| Horsley and Bailie[23] | 86 | 1988 | No | MDI | 6 | 40 | 54 | |
| Horsley and Bailie[23]† | 86 | 1988 | Yes | MDI | 46 | 39 | 15 | |
| Paterson and Crompton[24]† | 321 | 1976 | Yes | MDI | 86 | 6 | 8 | |
| Gayrard and Orehek[25] | 69 | 1990 | No | MDI | 28 | 13 | 59 | |
| Gayrard and Orehek[25]§ | 46 | 1990 | Yes | MDI | 52 | 11 | 37 | |
| Hilton[20] | 36 | 1990 | NS | Spacer device | 58 | 20 | 22 | |
| Pedersen et al[21] | 85 | 1986 | Yes | Spacer device | | | | 59 |
| Hilton[20] | 23 | 1990 | NS | Turbuhaler | 78 | 18 | 4 | |
| Hilton[20] | 26 | 1990 | NS | Diskhaler | 54 | 27 | 19 | |

*NS = not specified.
†The study's categories were reclassified as follows: faultless = good; doubtful or adequate = adequate; totally inadequate or probably inadequate = inadequate.
‡The study's categories were reclassified as follows: efficient = good; doubtful = adequate; inefficient = inadequate.
§The study's categories were reclassified as follows: correct = good; doubtful = adequate; incorrect = inadequate.

Melchor et al[33] showed an increase in peripheral lung deposition of salbutamol, but not in total lung deposition, with the use of a spacer device.

Proper inhalation technique can also significantly affect the amount of drug delivered to the lung. Newman et al[34] showed that for patients who could not coordinate inhalation and actuation at baseline (44% of the population), instruction improved lung deposition from 7.2 to 22.8%. Furthermore, before instruction, the patients who coordinated inhalation and actuation had a higher lung deposition (18.6%) than those who did not (7.2%).

## Discussion

In this paper, we examined three factors influencing the effectiveness of asthma treatment with ICSs in practice—patient compliance, inhalation technique, and lung aerosol deposition. We found that only a small percentage of the prescribed dose of an ICS is likely to reach the target organ, the lung, because of patient noncompliance with the prescribed dose, difficulty in correct use of the inhaler, and the ability of a properly used inhaler to deliver the drug to the lung.

As with any chronic disease, patient compliance is an important determinant of therapeutic success. Creer and Levstek[39] divide the factors that are correlated with noncompliance into four categories: patient variables, interactions between physician or medical staff and patients or family, medication characteristics, and nature of asthma. Our evaluation indicates that patients were more likely to underuse ICSs than overuse them. Some examples of factors related to noncompliance and inhaled drugs include patients taking long-term medication who stop treatment if they have not experienced an attack for an extended period.[39] The delayed clinical impact of ICSs compared with bronchodilator drugs may be an additional factor in noncompliance. The possibility of psychosocial issues in noncompliant patients should not be overlooked. Bosley et al[40] found in a prospective cohort that noncompliant patients had a significantly higher prevalence of depression than compliant patients. Noncompliant patients also had a higher, although not statistically significant, prevalence of anxiety.

There is conflicting evidence about the relationship between the number of inhalations prescribed per day and compliance rates. Two published studies supported the assumption that there is an inverse relationship between the number of inhalations prescribed per day and compliance.[17,41] However, this inverse relationship was not supported in studies by Bosley et al[3] and Toogood et al.[42]

Education has been shown to increase compliance with dosing regimens. The study by van der Palen et al[16] showed this using electronic monitoring for compliance. A recent meta-analysis of the effects of



Table 3—*Observed Errors in Inhalation Checklists**

MDI

| Factors | Pedersen et al[21] | Pederson et al[21] | van Beerendonk et al[26] | Manzella et al[11] | Epstein et al[27] | Horsley and Bailie[23] | Scott-Smith[28] | Nimmo et al[29] 1st Puff | Nimmo et al[29] 2nd Puff | Goodman et al[30] | Gayrard and Orehek[25] Untrained | Gayrard and Orehek[25] Trained |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of patients | 132 | 851 | 56 | 234 | 68 | 84 | | 20 | 19 | 59 | 69 | 46 |
| Remove cap, % | | | 5 | | 4 | 5 | | 0 | NA | | | |
| Shake inhaler, % | 49 | 34 | 57 | 15 | 29 | 32 | 18 | 10 | 32 | | | |
| Hold inhaler upright, % | | | 2 | | 12 | | | 0 | 0 | | | |
| Place mouthpiece of inhaler into one end of spacer, % | | | | 66 | | | | | | | | |
| Position inhaler with index finger on top and thumb supporting the bottom, % | | | | 19 | | | | | | | | |
| Exhale before firing, % | 45 | 51 | 66 | 23 | | 58 | 0 | 15 | 26 | | 75 | 41 |
| Tilt head back, % | 12 | 14 | | | 15 | 30 | | | | | | |
| Place spacer tube between teeth, % | | | | 30 | | 15 | | | | | | |
| Close mouth, % | | | | 25 | 13 | | | 0 | 0 | | | |
| Release medication, % | | | | 18 | | | 9 | | | | | |
| Begin to breathe in and then activate inhaler, % | 55 | 17 | 68 | | 34 | 40 | | 25 | 42 | 47 | 48 | 33 |
| Inhale slowly and deeply, % | 67 | 29 | 70 | 26 | 43 | | 45 | 40 | 47 | 39–42 | | |
| Hold breath, % | 42 | 39 | 53 | 31 | 43 | 66 | 59 | 25 | 32 | 24 | 67 | 41 |
| Breathe out through nose, % | | | | | 75 | | | | | | | |
| Breath released slowly, % | | | | | | 48 | | 20 | 32 | | | |
| Wait before taking next puff, % | | | | 54 | 23 | 46 | | 35 | NA | | | |

Other Inhalers

| Factors | Pederson et al[21] | van Beerendonk et al[26] | Dompeling et al[7] | Nimmo et al[29] 1st Puff | Nimmo et al[29] 2nd Puff | Watson[31]† |
|---|---|---|---|---|---|---|
| Number | 39 | 257 | 41 | 13 | 14 | 144 |
| Type of inhaler | Rotohaler | Mix of dry powder inhalers | Rotohaler | Diskhaler | Turbuhaler | Turbuhaler |
| Cover removed, % | | | | 0 | 0 | 2 |
| Loading drug substance, % | 15 | 14 | 0 | 15 | 0 | |
| Hold inhaler at correct angle, % | | 7 | 51 | 0 | 7 | 3 |
| Rotation sequence correct, % | 46 | | 0 | | 0 | 1 |
| Air inlets uncovered, % | 19 | | | | | 3 |
| Exhale before firing, % | 62 | 66 | 93 | 0 | 14 | 3 |
| Tilt head back, % | 13 | | 17 | | | |
| Drug capsule not emptied, % | 36 | | | 15 | 0 | |
| Place mouthpiece between lips, % | | 4 | | 15 | 0 | |
| Release medication, % | | | | | | |
| Inhale forcefully and deeply, % | 41 | 19 | 29 | 23 | 0 | |
| Hold breath, % | 49 | 53 | 76 | 23 | 14 | 4 |
| Breathe out through nose, % | | | | | | |
| Breath released slowly, % | | | | 8 | 14 | |
| Wait before repeating steps, % | | | | | | |

*If blank, error was not reported. NA = not applicable for second puff.
†After instruction, others are preinstruction.

psychoeducational care in adults with asthma by Devine[43] also showed improvements in self-reported and physician-assessed compliance associated with education programs.

Other routes of administration for anti-asthma drugs may improve compliance. Kelloway et al[44] found that compliance was higher with prescribed oral medications compared with inhaled anti-inflam-

matory medications for asthma. However, their study was a retrospective database study that compared oral theophylline with two inhaled anti-inflammatory medicines. Thus, in their study, higher compliance with the oral drug might have been related to more rapid impact of theophylline on symptoms rather than the mode of administration. It is also important to note that oral medications are not affected by two of the three factors discussed in this paper that may reduce drug effectiveness: inhalation technique and lung deposition. Well-designed prospective studies comparing oral and inhaled asthma therapies could help further to determine the importance of route of administration.

Evidence suggests that noncompliance has an effect on patient outcomes. For example, Horn et al[45] treated 160 patients for as long as 9 months with increasing doses of inhaled salbutamol and beclomethasone dipropionate. The authors found that patients whose conditions improved had higher urinary salbutamol concentrations compared with those with persistent problems.

The effectiveness of inhaler therapy also depends on the inhaler technique. Patients may not be adequately instructed in inhaler technique, thereby reducing the amount of drug delivered to the lungs.[30] Cochrane[2(p15)] states that "it is important to reinforce the simple concept that failure to instruct patients on how to use inhalers and to reinforce these instructions will decrease compliance, whatever the drug or inhalation device." Our study found that subjective assessments of inhalation technique by physicians provided a wide range of values in patients using the inhaler properly. Technique is highly dependent on the type of inhaler. In our evaluation, we found that patients using a Rotohaler and an MDI had similar rates of "inadequate" technique. However, patients using DPIs other than the Rotohaler, such as the Turbuhaler and the Diskhaler, had lower rates of "inadequate" technique. "DPIs. . . have the intrinsic advantage that there is a natural coordination between generation of the aerosol cloud and inspiration."[46] The lack of need for coordination of two activities by the patient using a DPI makes it more likely that their inhalation technique with these devices will be good. As expected, patient groups using a spacer in addition to an MDI had lower rates of "inadequate" technique than the majority of patient groups using an MDI alone.

Because physician rating of patient technique is subjective, other methods of evaluating patient technique are needed, particularly so that the measurement scale can be consistent across studies. The study by Goodman et al[30] is an example of a study using an objective technique for measuring inhaler skills, a computer sensing device.

Several studies have shown that education can have a large impact on the percentage of patients who use an inhaler correctly.[23,25] The study by Goodman et al,[30] using a computer sensing device, indicated that women may have a greater need for education on inhaler technique because of less effective use of the inhaler. They suggest that this problem with inhaler technique might explain why women experience more severe asthma symptoms than men. However, a recent study in a health maintenance organization population by Osborne et al[47] showed that women had more severe asthma symptoms but that their MDI technique was no different from that of the men when skills were ranked using a 10-item checklist. Osborne et al[47] suggest one possible reason for the difference in results could be that the electronic sensor is a more accurate measure of inhaler skills than the 10-item checklist.

Studies have shown that written instructions are not sufficient and that verbal instructions and demonstrations and practice sessions need to be included.[29] Simple teaching devices can be built to develop coordination skills needed with MDIs.[48] Patients also need to be checked periodically to make sure that their skills have not eroded over time.[29]

The goal of inhaled therapy is to deliver medication directly to the lungs. The patient is at an advantage if the amount of the drug reaching the lungs is maximized and the amount deposited on the oropharyngeal region is minimized. The likelihood of adverse events can be reduced by reducing the amount of drug that reaches the oropharynx.[49] Many factors affect the amount of drug that reaches the lung, including inhaler technique and inhaler type, fine particle dose, and particle distribution. Of the studies in our analysis, only about 7 to 23% of any drug delivered by an MDI enters the respiratory tract. The rest of the drug is either deposited in the oropharynx or swallowed, leading to potential systemic side effects. Studies have shown that the amount of drug delivered to the lungs can be almost doubled and that the amount of drug deposited in the oropharynx greatly reduced through the use of large-volume spacers.[15] A study using the Turbuhaler showed an increased in drug deposition in the lung.[37] Jackson and Lipworth[13] report two studies that have shown that the use of a Turbuhaler is associated with greater efficacy of ICSs. Thus, the increased deposition might be associated with increased drug efficacy.

The lung deposition studies reported in our article show mixed results and do not clearly demonstrate that one type of inhaler is superior to another for use with ICSs. There is a need for more research in this area. Lung deposition depends critically on particle dynamics and jet flow,[50] which vary with drug formulation, inhaler type, and patient inhaler technique. Large crossover studies will need to be designed that control for drug type and particle size as well as inhaler technique. The outcomes of such studies should be both direct measures of drug deposition as well as measures of patient outcomes.

A key to efficacy for ICSs for treatment of asthma is the amount of drug prescribed that reaches the target organ. This review of patient compliance, inhalation technique, and inhaler type demonstrates the importance of these three factors in the appropriate delivery of ICSs to the lung. Health-care providers should consider these factors when evaluating and prescribing asthma medications.

**Table 4—*Drug Delivered to Target Area: MDI****

| MDI | | | MDI With Spacer | | |
|---|---|---|---|---|---|
| Study | Drug MMD, μm | Fraction Deposited in Lung, % | Study | Drug MMD, μm | Fraction Deposited in Lung, % |
| Dolovich et al[18] (n = 12)† | Label 2.2† | 14 | Newman et al[33] (n = 9) | Label† 3.2 | 21 |
| Newman et al[33] (n = 9) | Label 3.2† | 9 | Melchor et al[35] (n = 9)¶ | Salbutamol 2.8–2.9 | 19–21 |
| Newman et al[34] (n = 18) | Salbutamol not specified | 7–23§<br>19–13‖ | | | |
| Melchor et al[35] (n = 21)¶ | Salbutamol 2.8–2.9 | 14–22 | | | |
| Zainudin et al[36] (n = 9) | Salbutamol + label† 2.3 | 11 | | | |
| Borgström et al[37] (n = 13) | Terbutaline, not specified | 8 | | | |
| Range | | 7–23 | Range | | 19–21 |

*MMD = mass median diameter for inhaled particle.
†Based on a maximum of 6.8% delivered to the right lung.
‡"Label" refers to a radiotracer attached to a nontherapeutic particle.
§For patients who could not coordinate inhalation and actuation, before and after instruction.
‖For patients who could coordinate inhalation and actuation, before and after instruction.
¶Range for asthma patients to healthy subjects.

**Table 5—*Drug Delivered to Target Area: Inhalers****

| Breath-Actuated Inhaler | | | DPI | | |
|---|---|---|---|---|---|
| Study | Drug MMD | Fraction Deposited in Lung, % | Study | Drug MMD, μm | Fraction Deposited in Lung, % |
| Newman et al[34] (n = 18) | Salbutamol, not specified | 18–21† | Melchor et al[35] (n = 29) | Salbutamol 2.7–3.0 | 11–12‡ |
| | | | Zainudin et al[36] (n = 9) | Salbutamol + label§ 2.3 | 9 |
| | | | Borgström et al[38] (n = 10) | Budesonide < 3–> 10 | 15–28‖ |
| | | | Borgström et al[37] (n = 13) | Terbutaline, not specified | 19–22¶ |
| Range | | 18–21 | Range | | 9–28 |

*MMD = mass median diameter for inhaled particles.
†Range for patients who could coordinate inhalation and actuation and those who could not after all were trained to use the autohaler.
‡Range for asthma patients and healthy subjects.
§"Label" refers to a radiotracer attached to a nontherapeutic particle.
‖Range for slow to fast inspiratory flow.
¶Range based on inhaled drug dose.

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